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EXAMINER
SAXE, S

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1807	11

LYON AND LYON
34TH FLOOR, 611 W. SIXTH STREET
LOS ANGELES, CA 90017

DATE MAILED: 03/03/92

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 3 pages
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-14 are rejected.

5. ☒ Claims 12 are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. The disclosure is objected to because of the following informalities:

A. On page 5, line 6, the sentence does not make sense as written.

B. On page 6, line 12, "Nat'l" should be "Natl.".

C. On page 9, line 27, "preferable" should be "preferably".

D. On page 11, line 28, "radio isotope" should be "radioisotope".

E. On page 13, line 24, "effect" should be "affect".

F. On page 13, line 28, page 13, line 31, and page 14, line 13, "$C_oT_{1/2}$" should be "$C_ot_{1/2}$".

G. On page 16, lines 5-8, reference is made to an application which has now been allowed. This should be amended to refer to the patent number and not to the application number.

H. On page 16, line 10, remove the comma at the end of the line as it is confusing.

Appropriate correction is required.

16. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Claims 7 and 11 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. Whereas a single-stranded probe has utility, there is no evident utility

for the nucleic acid hybrids claimed in claims 7 and 11 and no utility for the hybrids is disclosed in the specification.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

A. On page 11, line 20, cobalt is listed as an isotopic label but no specific isotope is mentioned.

B. On page 14, line 2, the specification refers to the half-life of hybridization. Hybridizations do not have half-lives. The statement should read "Thus, it is the concentration of probe times the time at which 50% of total hybridization occurs at that concentration."

C. On page 14, line 4, the word "hybrid" is used but it makes no sense in the context. Probably "target" is the correct word to use here.

D. On page 14, line 5, the number 0.0012 is used. From the series of numbers it would appear that 0.012, not 0.0012, is correct. A correction of or a confirmation of 0.0012 is

required.

E. Table I (pages 17-18) is confusing. The heading "2.5 x 10⁸ 3 probe" is not understandable and needs to be explained. There is no indication as to what the numbers in the 2 columns of results refer. If these are RLU the table should have appropriate headings. Also, in reference to Table I, what is the difference between CDC Streptococcus "equl" and CDC Streptococcus equl (the last 2 species in the table)? Are these actual species or some types of controls? They are probably Streptococcus equi. If so, make a correction.

F. Table II gives only one set of data and no mention is made as to whether the data are for probe I, probe II, probe III or a mixture of the probes. An explanation of this data is required. Also, there are 3 blank spaces in Table II in the RLU column. These need to be explained.

G. To avoid a new matter issue, basis in the original file disclosure should be pointed to or filing of a declaration under rule 132 and laboratory notebook pages evidencing the correct data is suggested.

H. The attempt to incorporate subject matter into this application by reference to U.S. application nos. 298765, 613603 and 644879 is improper because it has not been shown that the applications have common inventors or are commonly assigned. See M.P.E.P. 608.01(p)(B). Amendment of the disclosure is required.

The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or

agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157; In re Hawkins, 486 F.2d 579, 179 USPQ 163; In re Hawkins, 486 F.2d 577, 179 USPQ 167.

19. Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

20. Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to oligonucleotide probes as disclosed in claims 8-10. As written this claim could encompass antibodies to be used as probes to distinguish species of Streptococcus. No mention of antibodies is made in the specification and therefore no guidance or examples have been given. The preparation of antibodies is well known, but the preparation of an antibody specific to a single species of bacterium is very unpredictable. Amendment of the claim to indicate a nucleic acid probe is suggested.

21. Claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to probe 1. The data in Table I indicate that either probe 2 or probe 3 or both hybridize to Streptococcus "equl" and therefore do not distinguish S. pyogenes from S. "equl". The presence of an example which does not work indicates that the art is unpredictable and that the invention has not been enabled. A change of a single base can be enough to change the specificity of an oligonucleotide probe. The specification gives no working

examples other than probes I, II and III and gives no guidance on how to prepare other probes of as little as 50% complementarity to a variable region of ribosomal nucleic acid which will distinguish S. pyogenes from other Streptococcus species. See M.P.E.P. §§ 706.03(n) and 706.03(z).

22. Claims 1-6 and 11-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-5 are indefinite in using the phrase "able to" because the claim does not set forth under what conditions one would be able to distinguish S. pyogenes from other Streptococcus species. The claim would be better if rewritten as "A hybridization assay probe which distinguishes...".

B. Claim 1 is vague in that it is not clear whether the probe distinguishes S. pyogenes from some other Streptococcus species or from all other Streptococcus species.

C. Claim 4 is indefinite in the use of the expression "50% complementarity". Does the 50% have to be a continuous stretch of probe or can it be divided up along the probe, i.e. is this local or global complementarity? Also, this claim is confusing in stating "a variable region of ribonucleic acid in S. pyogenes". The ribonucleic acid in S. pyogenes presumably does not vary. The variation is in the comparison of ribonucleic acids between species of Streptococcus. The claim should be

rewritten to make this clearer.

D. Claim 6 is confusing because it has an improper Markush group due to the presence of the use of "or" and "and". The claim should be rewritten with the "or" removed wherever it occurs and an "and" added to replace the final "or".

E. Claim 6 is also indefinite because it describes the nucleotide polymer which can hybridize to S. pyogenes in terms of E. coli sequences to which the probe cannot hybridize. Since the sequences between S. pyogenes and E. coli are different, the corresponding regions between the two genuses are not particularly specified.

F. Claim 6 is also vague in the use of the phrase "in the region". It is not clear what are the limits of the region to which the claim refers. This phrase should be deleted.

G. Claims 7 and 11 are incorrect in stating a "hybrid formed between an oligonucleotide...and a nucleic acid sequence". The hybrid is composed of two oligonucleotides, not an oligonucleotide and a sequence.

H. Claim 11 is also confusing in stating a hybrid formed between a member of a group of oligonucleotides and their complements and a complementary sequence thereto. The first reference to complementary oligonucleotides should be deleted. As written you have the possibility of a complementary sequence forming a hybrid with itself.

I. Claim 11 is vague and indefinite in its use of the word

"substantially" because the word "substantially" is relative terminology undefined in the specification. Does substantially mean 50%, 90%, 99%, etc.?

J. Claim 12 is indefinite in not clearly stating whether the probe mix consists of all three polymers of claims 8, 9 and 10 or whether a mix of any two polymers is also possible.

K. Claim 13 is indefinite in stating "the" polymer of claim 8, 9 or 10 since each of claims 8, 9 and 10 refers to two polymers, the oligonucleotide as given in the claim and the complement.

L. Claim 14 is confusing because it has an improper Markush group. As stated, a single oligonucleotide has 6 different sequences. The "and" at the end of the claim needs to be changed to "or" to have a proper Markush group. See M.P.E.P. 706.03(y).

23. Claim 4 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. A probe of only 50% complementarity to a variable region of ribosomal nucleic acid in S. pyogenes will not hybridize specifically to S. pyogenes but will hybridize to other species as well under conditions which allow hybridization to S. pyogenes. This would, therefore, broaden, not limit, claim 1.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the

date of application for patent in the United States.

25. Claims 1, 2 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kilpper-Bälz and Schleifer (FEMS Microbiology Letters 24, 355-365 (1984)). In this paper are described hybridizations using 23S rRNAs as probes to distinguish between groups of bacteria including S. pyogenes as a member of one of the groups (see page 362, 1st column). Kilpper-Bälz and Schleifer have therefore used a hybridization probe to distinguish S. pyogenes from some other Streptococcus species as claimed in claim 1 and said probe is complementary to 23S rDNA as claimed in claims 2 and 5 (see page 362, first column).

26. Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Ludwig et al. (J. Gen. Microbiol. 131, 543-551 (1985)). Table I (pages 545-547) lists partial sequences for 16S rRNA for 11 strains of bacteria including S. pyogenes and 9 other Streptococcus species. Several of these sequences, e.g. the final 15-mer listed (see page 547, Table I), are unique to S. pyogenes. Those sequences which are unique to S. pyogenes do distinguish it from other Streptococcus species. Although these sequences are not used as or referred to as probes in the reference it is inherent that they can necessarily be used as probes.

27. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Scott and Fischetti (U.S. Patent # 4,784,948 (Nov. 15, 1988)). This reference teaches a DNA probe specific for the

M protein gene of several species of Streptococcus. Table 3 (columns 15 and 16) and column 16 indicate that this probe hybridizes to several species of Streptococcus including S. pyogenes but not to all Streptococcus species. Thus this reference discloses a probe which can distinguish between S. pyogenes and some other Streptococcus species.

28. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See M.P.E.P. § 608.01(n).

Claim 11 should be moved to the end of the claims because it is an independent claim which intervenes between claims 12-14 and claims 8-10 upon which claims 12-14 are dependent.

29. Claim 12 is objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See M.P.E.P. § 608.01(n). In the interest of compact prosecution, claim 12 has been examined on the merits. However correction of this claim is required..

30. Claims 6-14 are allowable over the prior art of record.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Saxe whose telephone number is (703) 308-4235.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

32. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

M. Moskowitz

MARGARET MOSKO...
SUPERVI...
PA...
GROUP 180